Alternative Dosing Schedules for Irinotecan


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Most of the clinical experience with irinotecan (CPT-11 [Camptosar]) has been with either a weekly or an every-3-week schedule. Recent phase I trials have explored new routes and schedules of administration. One approach

Introduction

Four factors must be taken into account in the development of new methods of administration for a topoisomerase I inhibitor (Table 1), such as irinotecan hydrochloride (CPT-11 [Camptosar]). First, the dosing schedule should optimize biological effects resulting in topoisomerase inhibition. These include not only exposure of the cells to the topoisomerase I inhibitor during the S-phase of the cell cycle and prolonged stabilization of the cleavable complex, but also periodic release of inhibition to avoid the downregulation of cellular topoisomerase I levels as a mechanism for drug resistance.[1]

The second factor that should be considered is camptothecin pharmacology. In the case of irinotecan, this would mean selection of a dosing schedule that generates the highest (and potentially most effective) plasma and intracellular levels of SN-38, the active metabolite of irinotecan. The schedule would also take into account ways in which the conversion of irinotecan to SN-38 could be maximized and the balance between SN-38 and its inactive metabolite, SN-38 glucuronide (SN-38G) could be optimized.

The third consideration in selecting a schedule of drug administration is toxicity. Some schedules may be associated with less severe (or different) toxicity profiles without a loss of efficacy. Lastly, pragmatic factors should be taken into account, including the regimen's cost, convenience, and ease of compliance. An additional pragmatic consideration is how well the schedule accommodates other drugs and/or modalities, such as radiation, that will be given with irinotecan.

Since the introduction of irinotecan into clinical trials more than a decade ago, a number of clinical strategies have been pursued in an attempt to identify the schedule with the optimal balance between clinical activity, safety, and convenience. The two schedules that have been used most often in phase II and III testing are: (1) the weekly schedule (most popular in the United States and Japan), in which the drug is administered once a week for 4 consecutive weeks, followed by 2 weeks of rest; and (2) the once-every-3-week schedule (the most commonly used schedule in Europe).[2]

Irinotecan, like all of the camptothecins, is considered a cell-cycle-specific drug. The lethal lesion is created when the DNA replication fork collides with a single-strand DNA break that has been created by topoisomerase I and has been stabilized (ie, not allowed to reseal) by the camptothecin analog. When the replication fork encounters the stabilized cleavable complex, the single-strand break is converted into an irreversible—and lethal—double-strand DNA break.[3] This is referred to as the "fork-collision" model. Given that cells must be in S-phase of the cell cycle for the fork collision to occur and that, at any given time, only a small percentage of cells are in S-phase, one could argue that more frequent (ie, weekly) dosing would be most desirable.

On the other hand, many drugs, including irinotecan, have a clear dose-response relationship in vitro.[4] This suggests that irinotecan should be given at the highest single dose possible in order to achieve maximal antitumor effect. This approach has been taken in the development of irinotecan in Europe, where the drug is most commonly administered at a dose of 350 mg/m² once every 3 weeks. In addition to exploiting the dose-response relationship, this approach has the added advantage of greater patient convenience, as it entails less frequent dosing than is required on a weekly schedule.
Alternative Dosing Strategies

As our knowledge of and experience with topoisomerase I inhibitors have increased, several new routes and schedules of drug administration have been explored in phase I trials.

Protracted Intravenous Dosing Schedule

One strategy that has been tested recently is a protracted intravenous (IV) dosing schedule.[5] Since the DNA-topoisomerase I cleavable complex is readily reversible, and the plasma half-life of SN-38, the active metabolite of irinotecan, is 13 to 15 hours, daily dosing may approximate the level of topoisomerase I inhibition achievable with continuous infusion but without the requirement for a central line or infusion pump. In addition, lower doses of irinotecan, given more frequently, could allow more complete glucuronidation to take place and result in decreased toxicity.[6] Lastly, in vitro and in vivo data suggest that camptothecin analogs may have enhanced activity and reduced toxicity when lower doses are administered more frequently.[7,8]

Saltz and colleagues from Memorial Sloan-Kettering Cancer Center performed a phase I trial in which patients were given intravenous irinotecan on a daily × 5 basis.[5] When the starting dose of 10 mg/m²/d for 5 days every 3 weeks proved to be tolerable, the duration of treatment was extended to 2 weeks, with treatment given on a Monday-through-Friday schedule (ie, 5 days on, 2 days off) every 3 weeks. A total of 21 patients were treated at dose levels of 10 to 22 mg/m²/d. Late-onset, grade 3 diarrhea and neutropenic fever were the dose-limiting toxicities (DLTs) at the 22-mg/m²/d dose level. Two patients with colorectal cancer had objective partial responses, and an additional six patients (five with colorectal cancer and one with soft-tissue sarcoma) achieved stable disease as their best response. The maximum tolerated dose (MTD)/recommended phase II dose was determined to be 17 mg/m² in heavily pretreated patients.

A follow-up study combining this daily IV dosing schedule with pelvic radiation in patients with locally advanced rectal cancer has been initiated.

Two ongoing trials are examining the toxicity and tolerability of low-dose, daily IV irinotecan in children. The Pediatric Oncology Group is evaluating irinotecan given daily × 5 every 3 weeks, while researchers at St. Jude Children’s Research Hospital are testing a daily × 5 schedule given every week for 4 consecutive weeks, followed by a 2-week rest. Both studies are performing detailed pharmacokinetic assessment.

An alternative approach with a similar rationale is being explored in an ongoing phase I trial at the National Cancer Institute. In this trial, irinotecan is being given as a 96-hour continuous IV infusion every 2 weeks.

Every-Two-Week Dosing Schedule

The finding of similar antitumor activity, but slightly different toxicity profiles, with the weekly and every-3-week schedules piqued interest in administering irinotecan once every 2 weeks to determine whether toxicity could be modified while antitumor activity was retained. A total of 51 patients were treated with irinotecan at dose levels ranging from 125 to 325 mg/m² administered every 2 weeks. Of the 51 patients, 41 (80%) had received prior chemotherapy and 20 (40%), prior radiation. The median number of prior chemotherapy regimens was 3 (range, 1 to 10).

Dose-limiting toxicity, in the form of grade 4 neutropenia and fever, occurred in two of two patients treated at the 300-mg/m² dose level. The study was amended to include granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]), 5 mg/kg subcutaneously on days 2 through 13. A second DLT of delayed, grade 3 diarrhea (one patient) and grade 3 vomiting despite optimal antiemetics (one patient) was defined for irinotecan at 325 mg/m² every 2 weeks (with G-CSF).

Non-dose-limiting grade 3 vomiting (acute and delayed) occurred at the 275-mg/m² dose level. A serotonin antagonist plus dexamethasone given before and for 3 days after chemotherapy effectively prevented this toxicity. Grade 3 diarrhea occurred in only 1 of 10 patients treated at the MTD/recommended phase II dose of irinotecan of 250 mg/m² (without G-CSF) and in none of 6 patients treated at the MTD/recommended phase II dose of irinotecan of 300 mg/m² (with G-CSF).

Pharmacokinetic analysis revealed a linear relationship between irinotecan dose and area under the concentration-time curves (AUCs) for irinotecan and, to a lesser extent, SN-38, suggesting that the peripheral conversion of irinotecan to SN-38 is not saturated at these doses. The AUC for SN-38G appeared to increase with irinotecan dose, suggesting that hepatic glucuronidation is not saturated at doses up to 325 mg/m².

Severe diarrhea was not a frequent toxicity with this schedule. No pharmacodynamic relationship between diarrhea and the AUCs for irinotecan, SN-38, or SN-38G was identified, and biliary index did not predict the occurrence of grade 3 or 4 diarrhea. Two patients with recurrent colorectal cancer achieved partial responses, lasting 6.8 and 13.4 months, and 26 patients had stable disease as their
best response. Although the spectrum of toxicity with the every-2-week schedule appeared to be similar to that observed with other irinotecan schedules, neutropenia and vomiting appeared to be more common in this trial, while delayed diarrhea seemed to be less common. The every-2-week schedule has now been tested in a phase II trial in patients with fluorouracil-refractory colorectal cancer and has demonstrated antitumor activity similar to that attained with a weekly or every-3-week schedule.\[9\]

**Oral Dosing Schedule**

As noted above, low-dose, daily administration of irinotecan has been shown to be more effective and less toxic than higher-dose, intermittent administration in vitro and in vivo.\[7,8\] However, the oral route of administration has several additional advantages. First, the oral route takes advantage of low gastric pH, which may favor retention of the drug in the active lactone ring configuration. Second, high concentrations of tissue carboxylesterases in the liver and gut should promote presystemic conversion of irinotecan to SN-38. This, coupled with the first-pass effect, should result in high concentrations of SN-38 in the liver, the most common site of colon cancer metastases. Lastly, the oral route should provide a convenient, cost-effective option for protracted dosing of irinotecan.

A phase I trial of short-course, oral irinotecan has now been completed. [Drengler RL et al, unpublished data, 1998] In this trial, the intravenous preparation of irinotecan was administered orally once daily for 5 consecutive days every 3 weeks. The safety, pharmacokinetics, and antitumor activity of irinotecan were assessed in 28 patients. Late-onset, grade 4 diarrhea, with or without concomitant grade 4 neutropenia, was the DLT. Different MTDs were defined for patients above and below the age of 65 years; the MTD (and recommended phase II dose) was 66 mg/m\(^2\)/d for patients < 65 years old and 50 mg/m\(^2\)/d for those ≥ 65 years old.

Several provocative observations were made regarding the pharmacokinetic behavior of irinotecan given by the oral route. There was an association between irinotecan dose and SN-38 pharmacokinetics, implying that there was no saturation of the enzymes responsible for the conversion of irinotecan to SN-38 when irinotecan was administered orally. There was a very high ratio of SN-38 AUC (both the total and glucuronide forms) to irinotecan AUC, suggesting that the oral route resulted in substantial presystemic conversion of irinotecan to SN-38. Lastly, more than two thirds of all the SN-38 present during the first 24 hours following drug administration was detectable in the active lactone ring form.

In addition to these important pharmacokinetic observations, clinical antitumor activity was also observed. One patient with previously treated colorectal cancer and liver metastases achieved a confirmed partial response, and an additional 17 patients experienced stable disease lasting from 2.5 to 14.7 months.

Several follow-up phase I studies using an encapsulated oral form of irinotecan have now been initiated.

**Conclusions**

The sound scientific rationale for exploring alternative dosing routes and schedules of irinotecan is being borne out by the data emerging from phase I trials. Although the spectrum of toxicity seen with new routes and schedules of administration does not appear to differ from that observed with the more traditional administration schedules, the relative frequency and severity of irinotecan-induced toxicities seem to vary with different routes and schedules. Antitumor activity has been observed in phase I trials using these newer approaches. As we gain more experience with the newer routes and schedules of drug administration, we can expect to see the emergence of more convenient, more effective combination chemotherapy and combined-modality treatment regimens using irinotecan.

**References:**


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